Veterinary Parasitology 266 (2019) 7–11

Contents lists available at ScienceDirect

Veterinary Parasitology

journal homepage: www.elsevier.com/locate/vetpar

Research paper

Anthelmintic activity of injectable eprinomectin (eprecis® 20 mg/mL) in naturally infected dairy sheep

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ARTICLE INFO

Keywords:
Dairy sheep
Gastrointestinal nematodes
Efficacy
Eprinomectin
Injectable
Formulation

ABSTRACT

The anthelmintic activity of an injectable eprinomectin formulation (Eprecis® 20 mg/mL) was evaluated in 150 naturally infected dairy sheep raised in 3 semi-intensive flocks. All ewes were at the same stage of lactation and grazed on natural pastures. Ewes did not receive any anthelmintic treatment for at least 4 months prior to the experiment. In each flock, 50 ewes were selected and randomly allocated to control (C) or treatment (T) groups (n = 25 per group). Groups were balanced according to the ewes' bodyweight (BW) and fecal egg count (FEC) measured seven days before eprinomectin administration (day-7). On study day 0, ewes in group T, received 0.2 mg/kg BW of eprinomectin subcutaneously (Eprecis® 20 mg/mL, Ceva). Ewes in group C were left untreated. Fecal samples were collected on day 0, 7, 14, 21 and 28 post-treatment to assess FEC and for coprocultures. Ewes were weighed on day 0 and 28. Overall and within-flock efficacy of eprinomectin was calculated throughout the experimental period. No local or general adverse reaction after injection was observed. The most prevalent parasite genera were Teladorsagia, Haemonchus and Trichostrongylus. Following treatment, the overall mean FEC of C and T groups differed significantly ($P < 0.001$). Overall and within-flock efficacy of eprinomectin was 99.8%–100.0% and 99.7%–100.0%, respectively. Contrary to C group, ewes treated with injectable eprinomectin increased their BW during the study (−0.5 kg vs. + 1.5 kg, $P < 0.001$). In this field study, a single subcutaneous injection of eprinomectin to dairy sheep, at 0.2 mg/kg BW, resulted in excellent curative anthelmintic activity; egg counts remain low for at least 28 days after treatment.

1. Introduction

In Greece, small ruminants are mainly raised for milk production. Around 80% of sheep flocks are reared under semi-intensive conditions; grazing on natural pastures year-round and supplemented with concentrates and alfalfa hay during winter. Under these conditions, sheep and especially lactating ewes are challenged with gastrointestinal nematodes which cause a reduction in voluntary feed intake, health problems and significant economic losses due to impaired milk production (Papadopoulos et al., 2003; Laurenson et al., 2011).

Control of endoparasites in lactating ewes is challenging. Considering that pasture management strategies are uncommon in Greek flocks, control of endoparasites depends heavily on anthelmintics. However, very few anthelmintics are licensed for lactating ewes. Albendazole is an option but, requires withdrawal of milk for at least four days. Hence, it is not used in lactating ewes but rather in dry ewes or after lambing. But. there is evidence in the literature suggests about significant anthelmintic resistance to benzimidazoles (Kaplan and Vidyashankar, 2012; Gallidis et al., 2012). Eprinomectin is proposed as a good option for the control of gastrointestinal nematodes in lactating ewes because it combines a zero day milk withdrawal period with a broad spectrum anthelmintic activity against gastrointestinal nematodes, lungworms and some ectoparasites (Cringoli et al., 2003). Eprinomectin is available as injectable solution for cattle at a dose rate of 0.2 mg/kg (Eprecis® 20 mg/mL, Ceva) and as pour on formulation for cattle and small ruminants at 0.5 or 1.0 mg/kg (Eprinex® Multi, Boehringer Ingelheim), respectively. Parenteral administration of eprinomectin appears to be preferable given the higher bioavailability (Briqué-Pellet et al., 2017) and the lower variability in drug exposure (EMA, 2017). Moreover, the topical use of eprinomectin in sheep is not

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https://doi.org/10.1016/j.vetpar.2018.12.014
Received 26 August 2018; Received in revised form 28 November 2018; Accepted 21 December 2018

easy in practice because requires the partial removal of fleece and direct contact of the applicator bottle spout on the skin over the backline (Eprinex® Multi 5 mg/mL, UK SPC, 2018). The injectable formulation is expected to deliver a more accurate dose of the anthelmintic. Early pharmacokinetic studies, conducted in sheep with experimental subcutaneous formulations, reported a good bioavailability and slow elimination of eprinomectin (Modi et al., 2014). However, these experimental formulations were not optimal and resulted in variable levels of absorption. In a recent pharmacokinetic and milk residue depletion study (Achard et al., 2017), lactating ewes that received the subcutaneous formulation Eprecis® 20 mg/mL at 0.2 mg/kg had mean plasma eprinomectin concentrations above the efficacy threshold throughout the study (7 days). Residue levels of eprinomectin in milk samples were below defined threshold levels (EMA, 2016). Considering the available literature, there is no evidence of research data from field studies regarding the efficacy of injectable eprinomectin in lactating ewes. Hence, the objective of this study was determine the anthelmintic efficacy a single subcutaneous dose of Eprecis® 20 mg/mL in lactating ewes that were naturally infected while grazing in natural pastures where they were also maintained for 28-days post-treatment.

2. Materials and methods

2.1. Farms, animals and experimental design

The experiment was conducted from January to March 2018 in 3 semi-intensive farms (A, B and C) in the region of Central Macedonia, Greece. The selected farms were representative of typical dairy sheep farms (Gelasakis et al., 2010). The farms raised flocks of pure-bred and cross-bred sheep of local dairy breeds (Chios and Lesvos), with an average milk yield of around 280 L per lactation (240 days).

One-hundred and fifty clinically healthy dairy ewes (50 per farm) were selected. They were in early to mid-stage of their 2nd–4th lactation with good body condition score ≥2.5 (0–5 grade scale). All ewes were milked twice per day. Their diet was based mainly on grazing natural pastures for at least 6 h per day throughout the duration of the study. A concentrate feed (up to 0.8 kg/ewe, divided in 2 portions) was offered twice a day in the milking parlor. They were also offered a fixed amount of alfalfa hay (up to 0.8 kg) and had ad libitum access to wheat straw and water. The estimated dry matter of concentrates, alfalfa hay and straw consumed by ewes was approximately 1.6 kg. The ewes were reared semi-intensively and produced approximately 1.5 L of milk daily. Considering their body weight and level of milk production their minimum dry matter intake was 2.25 kg. Hence, at least 30% of their daily dry matter intake was obtained from grazing. Ewes did not receive any anthelmintic in the 4 months prior to the experiment.

The timeframe of the study was determined by the designated date of Eprecis® 20 mg/mL, which was set as day 0. Seven days before (day-7), all ewes in each flock were weighed. Moreover, individual fecal samples were collected for fecal egg count (FEC) and coprocultures. The ewes were allocated to 2 groups (n = 25 each), designated as control, C and treatment, T, balanced for FEC and initial mean body weight (BW). All ewes were weighed again on study days 0 (for dose calculation) and 28 (for comparison with day-7 and day 0). On study day 0 (immediately after the morning milking) ewes in group T, received a single subcutaneous injection of Eprecis® 20 mg/mL at a dose rate of 0.2 mg/kg BW on the hairless axillary area, using 1 mL disposable syringes and 1.3 cm 18-gauge hypodermic needles. Ewes in group C were left untreated. After day 0, ewes of group C, were visually examined daily by the same veterinarian for signs of local or general adverse reactions to eprinomectin administration. All farmers gave informed consent regarding the inclusion of their animals in the study. The experiment was conducted in compliance with ethical and institutional guidelines set by the Research Committee of the Aristotle University of Thessaloniki (approval protocol number 95660).

2.2. Parasitological procedures

Individual fecal samples were collected from all ewes on study days-7, 0, 7, 14, 21 and 28. Immediately after collection, samples were kept in a cooler box and transferred within 2 h to the Laboratory of Parasitology and Parasitic Diseases where they were stored at 4–10 °C and analysed within 2 days. Individual FECs for strongyles parasite eggs were assessed using a quantitative modified McMaster technique (Coles et al., 2006) with a sensitivity of 50 eggs per gram of feces.

Moreover, pooled fecal samples from each farm at the designated samplings were processed for coprocultures. The pooled fecal samples contained equal amounts from all animals in a group. Nematode larvae were recovered using the Baermann technique, after an incubation period of 12 days at 22 °C (Roberts and O'Sullivan, 1950). Morphological identification of 100 parasitic nematode L3 larvae was performed according to morphological keys of Van Wyk and Mayhew (2013). In cases where less than 100 larvae were recovered, percentages are reported.

2.3. Statistical analysis

BW difference between day 28 and day 0 of groups C and T, both overall and within-flock, was compared using an independent samples t-test. The FECs between ewes of C and T groups were compared using the non-parametric Wilcoxon rank-sum test. Significance level was set at $P < 0.05$. Data were analyzed using IBM SPSS v.22.0 (Armonk, NY: IBM Corp.).

All FECs (count +1) were ln-transformed to calculate the geometric means. The overall and within-flock efficacy of Eprecis® 20 mg/mL on each sampling day was calculated as follows:

$$(\%)efficacy = 100 \times \frac{Cgm - Tgm}{Cgm}$$

where C_{gm} represents the geometric mean FEC for untreated ewes and T_{gm} the geometric mean FEC for treated ewes (Wood et al., 1995).

3. Results

Subcutaneous injection of Eprecis® 20 mg/mL was well tolerated by dairy ewes and no local or general adverse reactions were observed across the experiment.

A total of 9 ewes died during the study; 6 in group C and 3 in group T. Three ewes died from acute ruminal acidosis due to accidental grain overconsumption (Farm A) and six ewes (1 in Farm A and 5 in Farm B) died from acute mastitis. The available FEC data of these animals were kept in the statistical analysis while their BWs were excluded. One treated ewe from farm B lost its identification collar during the experiment. The data from this ewe were also excluded from data analysis.

The most prevalent parasites identified in this study were Teladorsagia spp., Haemonchus spp. and Trichostrongylus spp (Table 1). Proportionally, the identified species remained the same across the study. No indication of resistance of any species to eprinomectin was noted. At day 0, across all farms, the geometric mean FEC of group T (n = 327.3) was not different from the geometric mean FEC of group C (n = 266.3, P = 0.094; Table 2). From day 0 to day 28, the overall geometric mean FEC of the group C increased steadily (maximum of n = 842.3 at day 28) while it decreased in the group T (maximum of n = 1.8 at day 28). In each farm, the geometric mean FEC of the group T was persistently lower than the geometric mean FEC of the group C from day 7 to day 28 ($P < 0.001$). Overall, the efficacy of Eprecis® 20 mg/mL at days 7, 14, 21 and 28 post-administration was ≥99.8% (Table 2).

In all farms, the mean BW of control ewes decreased by 0.5 kg from day 0 to day 28 (Table 3). There was consistent decrease in the BW of ewes in group C in all farm. However. the mean BW of ewes in group T,

Table 1
Gastrointestinal nematode species identified from pooled fecal samples for a period of 28 days following a single subcutaneous eprinomectin injection (Day 0) in naturally exposed dairy ewes.

	Parasite species	Day-7[a]	Day 0	Day 7	Day 14	Day 21	Day 28
Farm A							
Control	*Teladorsagia spp.*	90	86	87	83	81	76
	Haemonchus spp.	9	12	9	14	15	21
	Trichostrongylus spp.	1	2	3	3	4	2
	Chabertia spp.	0	0	1	0	0	0
	Bunostomum spp.	0	0	0	0	0	1
Treated	*Teladorsagia spp.*	90	83	0	33.3	58.8	52
	Haemonchus spp.	9	11	0	66.7	35.3	39.6
	Trichostrongylus spp.	1	4	0	0	5.9	8.4
	Chabertia spp.	0	1	0	0	0	0
	Bunostomum spp.	0	0	0	0	0	0
Farm B							
Control	*Teladorsagia spp.*	62	56	62	57	53	54
	Haemonchus spp.	32	36	32	40	44	46
	Trichostrongylus spp.	6	8	4	3	3	0
	Chabertia spp.	0	0	1	0	0	0
	Bunostomum spp.	0	0	1	0	0	0
Treated	*Teladorsagia spp.*	62	61	0	0	54	52.5
	Haemonchus spp.	32	34	0	0	40	40.9
	Trichostrongylus spp.	6	4	0	0	4	6.6
	Chabertia spp.	0	0	0	0	0	0
	Bunostomum spp.	0	1	0	0	2	0
Farm C							
Control	*Teladorsagia spp.*	77	73	67	68	71	66
	Haemonchus spp.	16	22	29	26	27	31
	Trichostrongylus spp.	6	5	3	6	1	2
	Chabertia spp.	1	0	1	0	1	1
	Bunostomum spp.	0	0	0	0	0	0
Treated	*Teladorsagia spp.*	77	67	68.7	54.5	61.1	50
	Haemonchus spp.	16	30	31.3	45.5	38.9	40
	Trichostrongylus spp.	6	2	0	0	0	8
	Chabertia spp.	1	1	0	0	0	2
	Bunostomum spp.	0	0	0	0	0	0

[a] Coproculture on study day-7 was based on pooled samples from all ewes within a flock, before animal allocation to control or treated groups.

Table 2
Comparison of fecal egg counts (FEC) between control and treated with Eprecis® 20 mg/mL at 0.2 mg/kg BW naturally infected dairy ewes during a 28-days period post-administration.

			CONTROL GROUP			TREATED GROUP		Efficacy (%)
			Fecal egg count			Fecal egg count		
	Day*	n	GM	Range	n	GM	Range	
Farm A	−7	24	142.5	0–900	25	92.1	0–1300	
	0	25	156.4	0–900	25	187.4	0–1250	
	7	25	430.5[a]	100–1000	24	0.0[b]	0–0	100.0
	14	24	497.4[a]	100–1100	24	0.4[b]	0–50	99.9
	21	24	671.6[a]	350–1100	24	0.2[b]	0–50	100.0
	28	23	757.0[a]	100–1250	22	0.8[b]	0–100	99.9
Farm B	−7	25	199.8	0–800	24	330.3	50–950	
	0	25	226.6	0–800	24	351.7	0–1100	
	7	24	423.9[a]	200–900	24	0.0[b]	0–0	100.0
	14	21	567.4[a]	300–1000	23	0.0[b]	0–0	100.0
	21	21	704.0[a]	500–1200	23	0.7[b]	0–50	99.9
	28	21	820.5[a]	300–1250	23	2.2[b]	0–200	99.7
Farm C	−7	25	369.9	200–900	25	402.9	100–950	
	0	25	532.0	250–1000	25	521.5	300–1000	
	7	24	695.8[a]	450–1000	25	0.5[b]	0–150	99.9
	14	24	773.7[a]	500–1250	25	0.9[b]	0–50	99.9
	21	23	919.2[a]	600–1300	25	0.6[b]	0–100	99.9
	28	25	949.9[a]	100–1500	25	2.9[b]	0–150	99.7
All farms	−7	74	225.9	0–900	74	229.7	0–1300	
	0	75	266.3	0–1000	74	327.3	0–1250	
	7	73	501.6[a]	100–1000	73	0.1[b]	0–150	100.0
	14	69	603.7[a]	100–1250	72	0.4[b]	0–50	99.9
	21	68	757.8[a]	350–1300	72	0.5[b]	0–100	99.9
	28	69	842.3[a]	100–1500	70	1.8[b]	0–200	99.8

[a,b]FECs with different superscripts in the same row differed significantly ($P < 0.0001$).
* Day 0 represents the day of Eprecis® 20 mg/mL administration.

Table 3
Mean bodyweights (± SD) and weight gain of untreated and treated with Eprecis® 20 mg/mL at 0.2 mg/kg BW naturally infected dairy ewes during a 28-days period post-administration.

Farm	Group	*Study day 0		Study day 28		Weight gain (kg)	P-value
		n	Bodyweight (kg)	n	Bodyweight (kg)		
A	Control	23	46.5 (± 7.0)	23	46.3 (± 7.8)	−0.2	0.001
	Treated	23	42.8 (± 6.1)	23	45.5 (± 6.5)	+ 2.7	
B	Control	21	45.1 (± 6.9)	21	45.1 (± 7.1)	0.0	0.014
	Treated	23	44.9 (± 7.6)	23	46.3 (± 8.1)	+ 1.5	
C	Control	25	49.3 (± 5.7)	25	47.9 (± 5.6)	−1.4	0.03
	Treated	25	47.3 (± 6.1)	25	47.6 (± 4.7)	+ 0.3	
All	Control	69	47.0 (± 6.7)	69	46.4 (± 6.9)	−0.5	< 0.001
	Treated	71	45.0 (± 6.8)	71	46.5 (± 6.5)	+ 1.5	

* Study day 0 represents the day of Eprecis® 20 mg/mL administration.

increased by 1.5 kg from day 0 to day 28. The same pattern was observed in the 3 farms studied. The BW gain of treated ewes in Farm C was lower than that observed in the other farms; this might have been influenced by a diarrhea event, due to overgrazing in young vegetation after a rainfall and subsequent indigestion, in the last week of the study. The evolution of the BW gain from day 0 to day 28 between control ewes (−0.5 kg) and treated ewes (+1.5 kg) was significantly different ($P < 0.001$).

4. Discussion

The predominant gastrointestinal nematode species identified in the flocks of our study are in total agreement with the previously reported findings of an extended epidemiological study conducted in dairy sheep and goat farms in central and northern Greece (Papadopoulos et al., 2003). Moreover, the significant increase in the worm egg output of untreated ewes observed throughout the period of our study was also noted by the latter study, which found that the nematode infection intensity started to increase significantly from February and peaked during spring. The sharp increase during this period can be attributed to a periparturient immunity relaxation of the host and/or to a seasonal rise due to higher rainfall and temperature levels during spring, favoring parasite survival, and increased grazing time, augmenting the risk of infection (Papadopoulos et al., 2003).

The high anthelmintic efficacy of eprinomectin has been well documented in cattle (Rehbein et al., 2012), sheep (Hamel et al., 2017) and goats (Rehbein et al., 2014) treated with pour-on formulations at a dosage of 0.5 mg/kg BW and 1.0 mg/kg BW, as suggested for cattle and small ruminants, respectively. However, the length of fleece in sheep and hair in goats, and the licking/grooming behavior, although limited in these species compared to cattle, have been identified as factors compromising drug delivery and/or efficacy (Bousquet-Mélou et al., 2011). Applying the bottle spout against the skin after parting or shearing the fleece to obtain a more reliable drug delivery has practical difficulties, especially in sheep. An alternative option, administration of the topical formulation via the oral route, has been investigated and showed good anthelmintic efficacy in goats and sheep (Badie et al., 2015; Esteves Lopes et al., 2017). But, the suitability and safety of the excipients included in the pour-on formulation for oral application and the relevant meat and milk residue levels were not reported in those studies.

The anthelmintic efficacy of injectable eprinomectin formulations has been confirmed in experimentally infected beef cattle (Soll et al., 2013), in naturally infected beef cattle and in experimentally infected dairy goats (Briqué-Pellet et al., 2017). Considering the latter studies and the available literature, the present study is the first one assessing the effectiveness of injectable eprinomectin in naturally infected dairy sheep grazing in natural pastures. The results showed that ewes faced a continuous parasitic challenge during the experiment that caused more than a 2-fold increase of mean FEC in the untreated group. In treated ewes the overall efficacy remained high during the 28 days of the study. The overall BW gain observed in group T indicates a significant beneficial outcome of eprinomectin administration in dairy ewes at/or around the peak of their lactation. The notion is that from lambing up to peak of lactation, dairy ewes usually lose body condition due to low dry matter intake and increased energy and protein requirements for milk production (Cannas, 2004). Hence, elimination of the gastrointestinal worm burden at this stage of lactation is likely to increase nutrient utilization towards milk production and faster reconstitution of body fat and protein reserves.

5. Conclusion

A single subcutaneous injection of eprinomectin in naturally infected dairy ewes grazing in natural pastures was well tolerated and showed excellent curative anthelmintic activity; egg counts remain low for at least 28 days after treatment. Moreover, treated animals benefited because their BW increased throughout the experimental period.

Conflict of interest statement

The present study was funded by Ceva Santé Animale, France. Authors state that data handling and results were evaluated independently without any interference by the sponsors.

Acknowledgements

The authors would like to thank Dr Clare Squires for providing useful and structural comments that improved the quality of the manuscript.

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